



# Normalization of ADC does not improve correlation with overall survival in patients with high-grade glioma (HGG)

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## Abstract

Mixed reports leave uncertainty about whether normalization of apparent diffusion coefficient (ADC) to a within-subject white matter reference is necessary for assessment of tumor cellularity. We tested whether normalization improves the previously reported correlation of resection margin ADC with 15-month overall survival (OS) in HGG patients. Spin-echo echo-planar DWI was retrieved from 3 T MRI acquired between maximal resection and radiation in 37 adults with new-onset HGG (25 glioblastoma; 12 anaplastic astrocytoma). ADC maps were produced with the FSL DTIFIT tool (Oxford Centre for Functional MRI). 3 neuroradiologists manually selected regions of interest (ROI) in normal appearing white matter (NAWM) and in non-enhancing tumor (NT) <2 cm from the margin of residual enhancing tumor or resection cavity. Normalized ADC (nADC) was computed as the ratio of absolute NT ADC to NAWM ADC. Reproducibility of nADC and absolute ADC among the readers' ROI was assessed using intra-class correlation coefficient (ICC) and within-subject coefficient of variation (wCV). Correlations of ADC and nADC with OS were compared using receiver operating characteristics (ROC) analysis. A p value 0.05 was considered statistically significant. Both mean ADC and nADC differed significantly between patients subgrouped by 15-month OS (p = 0.0014 and 0.0073 respectively). wCV and ICC among the readers were similar for absolute and normalized ADC. In ROC analysis of correlation with OS, nADC did not perform significantly better than absolute ADC. Normalization does not significantly improve the correlation of absolute ADC with OS in HGG, suggesting that normalization is not necessary for clinical or research ADC analysis in HGG patients.

**Keywords** Diffusion weighted imaging (DWI) · Apparent diffusion coefficient (ADC) · ADC normalization · High-grade glioma (HGG)

## Introduction

High-grade gliomas (HGG) are the most common and aggressive of primary brain tumors. MRI is the primary modality used widely for diagnosis and assessment of treatment response in HGG [1].

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Diffusion weighted imaging (DWI) is one of the most mature advanced MRI techniques used in conjunction with conventional anatomic MRI to probe brain tumor tissue physiology and function. Apparent diffusion coefficient (ADC) maps generated from DWI reflect microscopic, sub-voxel level barriers to the random thermal motion of water molecules in each image voxel [2, 3]. Because the principle barriers to water diffusion in brain and tumor tissue are intracellular and cell membranes, tissue ADC measured with clinical DWI—typically employing a diffusion sensitization gradient “b-value” of  $1000 \text{ s/mm}^2$ —is largely determined by the extracellular volume fraction, which itself represents a convolution of tissue cellularity, tissue edema and tissue necrosis. The use of ADC as an indicator for HGG response is appealing because DWI is rapid, relatively motion insensitive, technically robust and does not require use of a contrast agent. Multiple studies have demonstrated that low pre-treatment minimum tumor ADC ( $\text{ADC}_{\min}$ ) correlates with high cellularity and that  $\text{ADC}_{\min}$  correlates with survival in HGG patients [4, 5]. The published optimal  $\text{ADC}_{\min}$  thresholds for distinguishing highly cellular, high-grade tumor from lower cellularity and histological grade tumor range from  $0.6$  to  $1 \times 10^{-3} \text{ mm}^2/\text{s}$  [4–7]. Mean ADC values ( $\text{ADC}_{\text{mean}}$ ) have also been shown to correlate with overall survival (OS) at a cutoff value of  $1.04 \times 10^{-3} \text{ mm}^2/\text{s}$  [8]. Furthermore,  $\text{ADC}_{\text{mean}}$  has also been used to differentiate recurrent tumors ( $1.18 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$ ) from pseudoprogression and radiation-induced necrosis ( $1.40 \pm 0.17 \times 10^{-3} \text{ mm}^2/\text{s}$ ) [9].

Normalization of ADC was first reported in 2002 in order to reduce inter-scanner and inter-scan variation in ADC in the context of correlating ADC with histological measures of cellularity [10]. A number of researchers have more recently employed ADC normalization in the attempt to address the inconsistency in thresholds reported for  $\text{ADC}_{\min}$  and  $\text{ADC}_{\text{mean}}$ . Normalized ADC (nADC) values are calculated as the ratio of the ADC in the tumor to the ADC in normal-appearing contralateral white matter (NAWM), allowing the patient to serve as his or her own control [11, 12]. One study ( $n = 52$ ) reported that nADC has a stronger correlation with both progression-free survival (PFS) and OS than absolute ADC [13]. Another study ( $n = 18$ ) demonstrated that normalization improves differentiation of responders from non-responders in high-grade pediatric brain tumors [14]. Several other studies have reported significant correlation of nADC with survival but have not compared nADC directly to absolute ADC [11, 15].

Whether ADC normalization is necessary remains uncertain. In large part this depends on the relative reproducibility of absolute and nADC measurements. The reported cutoff values for  $\text{nADC}_{\min}$  ( $0.3$ – $0.75$ ) [13, 15] and the more reproducible  $\text{nADC}_{\text{mean}}$  ( $1.5$ – $1.62$ ) [9, 11] may seem small in absolute terms, but this must be compared to the known

very high reproducibility of ADC in volunteers and stroke patients. A multicenter (seven institutions), multi-vendor (GE, Philips, Siemens and Toshiba) and multi-field strength (1.5 and 3 T) investigation of gray and white matter ADC in stroke patients revealed an intra-vendor variation of 3–5% and inter-vendor variation of up to 15% in absolute ADC despite use of nearly identical scanning protocols and parameters [16]. The authors suggested that nADC may be essential to reduce this variation. However, of the four major vendors in their study one produced ADC estimates reproducibly lower than the other 3. When this was eliminated the inter-vendor variation dropped to roughly 7%. A more recent multicenter, DWI reproducibility study of healthy volunteers revealed inter- and intra-scanner coefficients of variance (CV)  $< 7\%$  across eight scanners, two vendors, two field strengths (1.5 and 3 T) and five centers [17]. Although the authors did not attempt to harmonize the DWI acquisition parameters other than b values (0 and 1000), both intra- and inter-scanner reproducibility were comparable, with only marginally inferior inter-scanner reproducibility.

The formulae for the ADC calculation itself incorporates signal intensities at 2 or more b-values, which introduces a substantial degree of intrinsic normalization. When combined with known very high reproducibility of absolute ADC measurements across patients and scanners from most major vendors this raises some question about the benefit to be expected from an additional normalization step. Given the minimal available published data comparing nADC to absolute ADC in brain tumor we set out to test whether nADC is superior to absolute ADC in a clinically representative group of HGG patients who had undergone a number of different treatments and had known survival. Our null hypothesis was that normalization of ADC in a clinical HGG population would not significantly improve the previously published correlation of ADC with the clinical gold standard of patient OS.

## Materials and methods

### Patients

A total of 37 HGG patients were included in this study, among which 25 patients had glioblastoma multiforme (GBM) and 12 had anaplastic astrocytoma (AA). The detailed patient selection criteria and treatment histories of this dataset have been reported previously in a paper reporting a strong correlation between pre-treatment non-enhancing tumor (NT)  $\text{ADC}_{\text{mean}} < 1.04 \times 10^{-3} \text{ mm}^2/\text{s}$  with a shorter OS ( $< 15$  months) compared to patients with a higher  $\text{ADC}_{\text{mean}}$  [8]. These pre-treatment DWI were acquired 3 days to 1 month after tumor resection surgery, and 3–7 days prior to chemo-radiation therapy. Because of the known strong

correlation of absolute  $ADC_{mean}$  with OS in this cohort, we analyzed normalized and absolute pre-treatment  $ADC_{mean}$ .

### Image acquisition and analysis

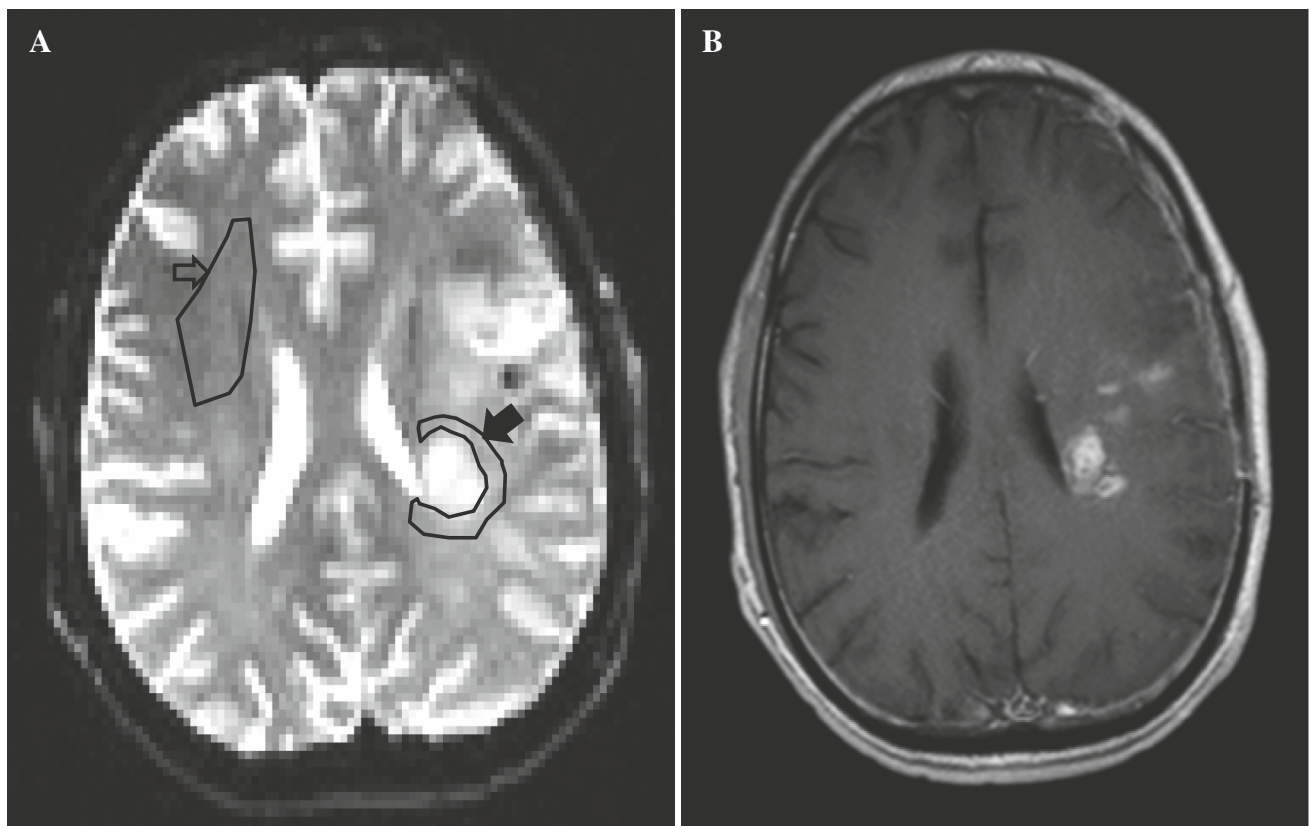
Data were acquired with one of several 3 T MR scanners in a single institution (SiemensHealthcare, Trio, Germany, and GE Medical Systems, Waukesha, WI), using three different product sequence DWI acquisition protocols, with detailed scan parameters reported previously [8]. Although scan parameters were not identical, the b-values were 0 and 1000 s/mm<sup>2</sup> for all acquisitions, and the correlation with OS of measured  $ADC_{mean}$  did not differ significantly between the protocols [8].

Three neuroradiologists independently selected the NT region in each case, defined as brain tissue located within 2 cm from the enhancing tumor or resection cavity on one representative slice. Regions of interest (ROIs) were manually outlined, and the mean ADC inside the ROIs was used for analysis [8]. The NAWM ROI was selected independently as well in the contralateral NAWM, or when no normal appearing contralateral white matter could be found, in an ipsilateral part of the white matter that appeared completely normal on MRI and that was some distance

away from any visible abnormality. This control ROI was selected so as to avoid large vessels, CSF and gray matter (Fig. 1).  $nADC_{mean}$  was calculated as the ratio of the absolute  $ADC_{mean}$  inside NT ROI to that in NAWM ROI.

### Statistical analysis

Mean and standard deviation (SD) of absolute and  $nADC_{mean}$  values were calculated for the three radiologists. Paired t-tests were used to compare the differences between readers. A mixed effects model taking readers as fixed effect and subjects (i.e. patients) as random effect was built to assess the repeatability across readers [18]. Within subject coefficient of variation (wCV) was calculated to measure relative repeatability of ADC measurement within each patient scan and intra-class correlation coefficient (ICC) was used to assess the inter-observer agreement between readers across the cohort [18, 19]. A receiver operating characteristics (ROC) curve was calculated to correlate  $ADC_{mean}$  and  $nADC_{mean}$  with the 15-month OS. The survival cutoff of 15 months was selected based on literature reporting 12–15 months median post-operative OS in GBM patients [20]. ROC analysis was also performed on subgroups of patients with GBM and AA respectively. Absolute ADC and  $nADC$



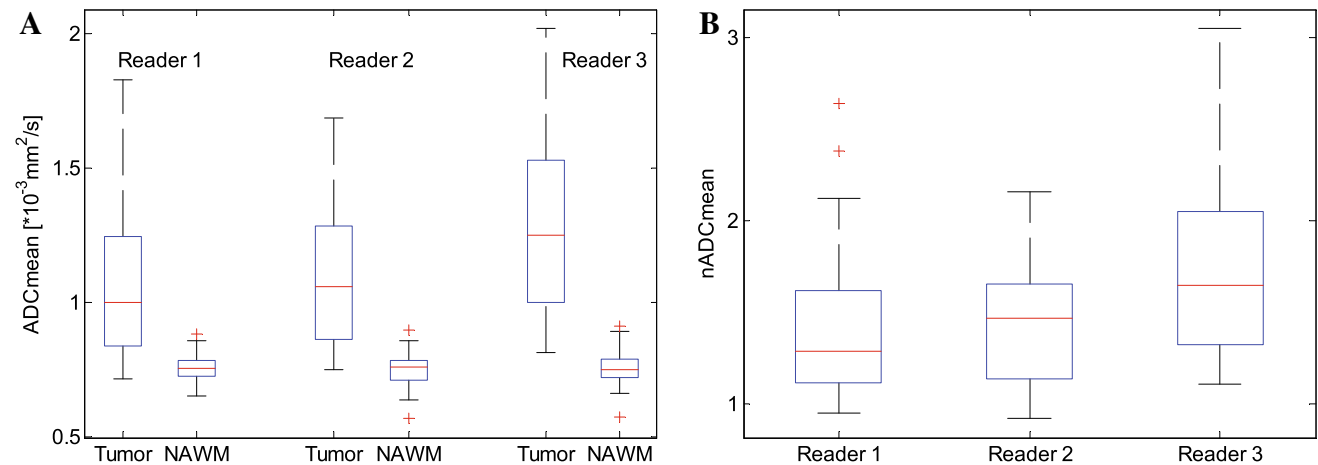
**Fig. 1** Representative ADC map (a) and post contrast T1 weighted (b) MRI. NAWM ROI is selected in the anterior right frontal lobe (hollow arrow) and NT ROI in the WM around the left fronto-parietal junction enhancing tumor (solid arrow)

**Table 1** With-in subject coefficient of variation (wCV) and ICC among three independent readers for absolute  $ADC_{mean}$  ( $\times 10^{-3} \text{ mm}^2/\text{s}$ ), NAWM  $ADC_{mean}$  ( $\times 10^{-3} \text{ mm}^2/\text{s}$ ) and  $nADC_{mean}$ 

	Reader 1	Reader 2	Reader 3	wCV%	ICC
NT $ADC_{mean}$ ( $\times 10^{-3} \text{ mm}^2/\text{s}$ )	$1.083 \pm 0.259$	$1.089 \pm 0.249$	$1.290 \pm 0.315^*$	15.9	0.60
NT $nADC_{mean}$	$1.439 \pm 0.433$	$1.450 \pm 0.331$	$1.712 \pm 0.448^*$	16.4	0.62
NAWM $ADC_{mean}$ ( $\times 10^{-3} \text{ mm}^2/\text{s}$ )	$0.759 \pm 0.047$	$0.754 \pm 0.065$	$0.758 \pm 0.064$	4.9	0.61

All data are represented as mean  $\pm$  standard deviation (SD)

\*Paired t-test shows  $p < 0.05$



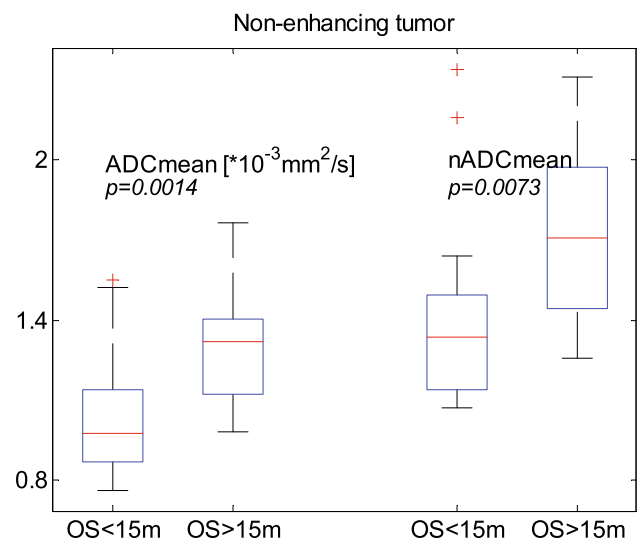
**Fig. 2** a The  $ADC_{mean}$  measured in tumor and NAWM by the three independent readers. b  $nADC_{mean}$  of the same readers

correlation with OS were compared within and between these subgroups. All statistical tests were performed using Stata Version 13 (StataCorp, Texas, USA). A  $p \leq 0.05$  was considered to be statistically significant.

## Results

Tumor  $ADC_{mean}$  was measured to be  $1.083 \pm 0.259$ ,  $1.089 \pm 0.249$ , and  $1.290 \pm 0.315$  (mean  $\pm$  SD) by the three readers respectively (Table 1). Readers 1 and 2 produced similar measurements, but Reader 3 produced significantly different measurements (Table 1; Fig. 2). NAWM  $ADC_{mean}$  was similar across the readers (Table 1). As a result, the  $nADC_{mean}$  of Reader 3 is significantly different from the other two readers and normalization did not improve variation among readers. wCV among the three readers were similar for both absolute and  $nADC_{mean}$ , at 15.9 and 16.4% respectively. The wCV of NAWM was much smaller at 4.9%. The ICC across readers was 0.61 [0.60–0.62] for all three metrics.

Figure 3 illustrates the  $ADC_{mean}$  and  $nADC_{mean}$  of patients categorized by OS less or greater than 15-months. T-tests demonstrate a significant difference between the survival



**Fig. 3** Box and whisker plots of the  $ADC_{mean}$  and  $nADC_{mean}$  of patients subdivided by 15-month OS. t-test shows that both  $ADC_{mean}$  and  $nADC_{mean}$  differed significantly between the two survival groups. Left is absolute  $ADC_{mean}$ ; t-test between the two groups shows a  $p = 0.0014$ . Right is  $nADC_{mean}$ ; t-test has a  $p = 0.0073$ . On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to cover  $\pm 2.7\sigma$  of data, and the crosses “+” denote the outliers

groups for both the  $ADC_{mean}$  and  $nADC_{mean}$  ( $p=0.0014$  and  $0.0073$  respectively) suggesting either can be used as a good biomarker for survival. In contrast to previous reports however,  $nADC$  did not detectably decrease the overlap in  $ADC$  distributions between the  $OS > 15$  m and  $OS < 15$  m groups [9].

Table 2 provides the summary statistics for the correlation between  $ADC_{mean}$  and  $nADC_{mean}$  with 15-month OS. ROC analysis shows that the  $nADC_{mean}$  correlation with OS was not significantly better than absolute  $ADC_{mean}$  correlation with OS.  $ADC$  estimates from Readers 1 and 2 correlate with OS significantly, but Reader 3 estimates did not. Normalization of  $ADC_{mean}$  did not improve the ROC AUC ( $p=0.19$ ). Subgroup ROC analysis revealed no significant difference between absolute  $ADC_{mean}$  and  $nADC_{mean}$  for either GBM (AUC=0.89 for both  $ADC_{mean}$  and  $nADC_{mean}$ ) or AA (AUC=0.79 for  $ADC_{mean}$  and AUC=0.75 for  $nADC_{mean}$ ) patients. Although the AUC for the GBM subgroup was slightly higher than for the AA subgroup, the difference was not significant ( $p=0.53$  for absolute  $ADC$ ;  $p=0.36$  for  $nADC$ ).

## Discussion

DWI estimates of  $ADC$  in HGG offers a valuable marker of tumor. Image voxels containing more cellular tumor have a smaller volume fraction of extracellular extravascular water and thus lower  $ADC$ . Conversely, voxels containing less cellular tumor have a higher extracellular volume fraction and thus higher  $ADC$ .  $ADC$  has been shown to correlate with cellularity, treatments response and prognosis in patients with HGG. A low  $ADC_{min}$  predicts a less favorable prognosis compared with a high  $ADC_{min}$  [4, 5]. Murakami et al. found the  $ADC_{min}$  to be a useful clinical prognostic biomarker for survival in 79 patients with

malignant supratentorial astrocytoma showing those with a low  $ADC_{min}$  ( $< 1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ ) having a poor prognosis [4]. Yamasaki et al. also found  $ADC_{min}$  to be a statistically significant correlate for OS in 33 GBM patients at a cutoff value of  $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$  [5]. Nakamura et al. revealed a pre-treatment cutoff value for  $ADC_{min}$  at  $0.93 \times 10^{-3} \text{ mm}^2/\text{s}$  to be able to predict survival in postoperative GBM patients [6]. While Saksena et al. demonstrated that patients with a pre-treatment  $ADC_{min} > 0.6 \times 10^{-3} \text{ mm}^2/\text{s}$  had a higher rate of progression free survival at 6 months compared to those with lower  $ADC_{min}$ , this finding was not statistically significant [7].

With varying  $ADC$  cutoff measures reported to correlate with survival, some investigators have proposed using  $nADC$  values instead of absolute values. Elson et al. evaluated postoperative MRIs of 52 GBM patients and found  $nADC_{min}$  measured within the T2/FLAIR volume to be the strongest predictor of PFS and OS when compared to absolute  $ADC_{mean}$ ,  $ADC_{min}$  and  $nADC_{mean}$ . A lower  $nADC_{min}$  ( $< 0.3$ ) was associated with poor survival [13]. Oh et al. revealed, in 28 postoperative GBM patients, a statistically significant shorter median survival time with an  $nADC_{mean} < 1.5$  compared to those with an  $nADC_{mean} > 1.5$  within the T2 region (11.2 and 21.7 months, respectively,  $p=0.004$ ) [11]. The  $nADC_{min}$  reported by Elson et al. is much smaller, but the  $nADC_{mean}$  of 1.7 is similar to the 1.5 cutoff value reported by Oh et al. Elson et al. showed that patients with an  $nADC_{mean} < 1.7$  have an inferior PFS and OS compared to those with  $nADC_{mean} > 1.7$  (4.4 vs. 7.9 months, and 11.7 vs. 15.5 months, respectively), however, this was not statistically significant. Hein et al. demonstrated that both  $ADC_{mean}$  and  $nADC_{mean}$  within enhancing lesions showed statistically significant lower values in the tumor recurrence or progression group compared to the non-recurrence group in a total of 18 patients with HGG. However, while  $nADC_{mean}$  showed no overlapping between the two groups at a cutoff value of 1.62 there was some overlap in the  $ADC_{mean}$  between the two groups [9]. Shankar analyzed 84 GBM patients' pre-treatment MRI and found that a cutoff  $nADC_{min}$  of 0.75 significantly correlated with OS [15], while absolute  $ADC_{min}$  or  $ADC_{mean}$  did not significantly correlate with survival.

Our findings are at odds with several recent publications suggesting that normalization of HGG tumor  $ADC$  improves correlation with survival and reduces variation in tumor  $ADC$  estimates. In our cohort, normalization of  $ADC$  did not improve correlation with OS compared to absolute  $ADC$  (Table 2). Nor did normalization reduce the variation among our three independent readers (Fig. 2). The wCV for tumor  $ADC_{mean}$  and  $nADC_{mean}$  estimates within each subject were almost the same at 15.9 and 16.4% respectively. Interestingly, from Table 1 and Fig. 2, one can clearly see that NAWM  $ADC$  measurements were much more consistent (wCV as low as 4.9%) across the readers compared to tumor

**Table 2** ROC curve correlating  $ADC$  with 15-month OS

	$ADC_{mean}$ ROC AUC $\pm$ std err ( $p$ value)	$nADC_{mean}$ ROC AUC $\pm$ std err ( $p$ value)
Reader 1	$0.8794 \pm 0.0647$ ( $< 0.0001$ )	$0.8618 \pm 0.0690$ ( $< 0.0001$ )
Reader 2	$0.8441 \pm 0.0708$ ( $< 0.0001$ )	$0.8353 \pm 0.0683$ ( $< 0.0001$ )
Reader 3	$0.6588 \pm 0.0920$ (0.08)	$0.6235 \pm 0.0949$ (0.19)
Mean <sup>a</sup>	$0.8206 \pm 0.0738$ ( $< 0.0001$ )	$0.7882 \pm 0.0781$ (0.0002)

AUC area under the curve

<sup>a</sup>Mean  $ADC_{mean}$  or mean  $nADC_{mean}$  is the average among the three readers

ADC even though all ROIs were defined independently. The observation that wCV of ADC measured in tumor is much higher than ADC measured in NAWM likely can be attributed in large part to the heterogeneous nature of HGG. This heterogeneity means that any slight difference in location of the ROI selection would result in a larger difference in ADC measurements than in NAWM. This probably explains why one of the readers measured significant different tumor  $ADC_{\text{mean}}$  compared to the other two readers. However, the mean of NAWM measured by the three readers are very consistent, 0.759, 0.754 and  $0.758 \times 10^{-3} \text{ mm}^2/\text{s}$  respectively. This is in good accordance with the literature: Grech-Sollars et al. measured a mean ADC of  $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$  for white matter in volunteers in a multicenter study [17] and Sasaki et al. measured similar WM mean ADC in their multivendor, multi-institutional study [16].

Normalization to NAWM is well suited to address variation between scans and between patients that affects the entire pulse sequence or image; in other words, variation that affects normal white matter voxels in the same way and to the same degree as tumor voxels. These include stochastic variation between measurements, normal anatomic variation, differences in coil coupling efficiency, pre-amplification, pulse sequence software, scanner hardware among others. However, the high reproducibility of NAWM ADC measurements, and more than threefold greater variation in tumor ADC measurements implies that sources of variation that affect NAWM and tumor voxels equally account for less than one-third of the overall variation observed in tumor ADC. As such it is not surprising that normalization of ADC did not detectably improve reproducibility of ADC measurements between readers or within subjects in our cohort.

The subgroup analysis supported the finding of equivalence between absolute and nADC demonstrated in the overall cohort: no significantly different was detected between absolute ADC and nADC correlation with OS when either AA or GBM patients were analyzed independently. The correlation of ADC and nADC with OS was very strong in each group. The AUC was slightly larger in the subgroup of GBM patients analyzed alone (0.89 ADC; 0.89 nADC) compared with the overall GBM and AA cohort (0.82 ADC; 0.79 nADC) and the AA patients analyzed alone (0.79 ADC; 0.75 nADC), although these differences did not reach statistical significance. This trend may reflect that the longer OS of AA patients compared to GBM patients weakened the statistical correlation in the AA subgroup, or could be related to differences in cellularity, vascularity, treatment or other factors between AA and GBM subgroups.

One limitation of our study is limited sample size. It is possible that a larger sample size would have revealed an effect of normalization we did not detect, but such an effect would not likely be large. We did not attempt to control for molecular markers, adjuvant or experimental therapies or

any of the other myriad factors that influence OS. Instead we deliberately included a population of patients with genetically and molecularly different tumors and different treatment histories. Our goal was to assess whether normalization improves the known correlation of ADC with survival, not to investigate the absolute correlation of ADC with survival. Within individual patients and the test population as a whole, differences in molecular tumor subtypes and therapies should not bias the comparison between ADC and nADC because the same ADC and OS data was used regardless of whether the ADC was normalized. While analysis of a homogeneous population might be expected to produce a higher absolute correlation between ADC and OS, normalization would be expected to provide greater benefit in a heterogeneous population. Also the heterogeneous population better mimics the heterogeneity encountered in real clinical populations and makes the result more readily generalizable to different clinical research populations. A patient population with greater homogeneity of tumor grade and treatment history might have allowed detection of a small effect that was not seen in our heterogeneous clinical sample, but such a study would be less directly applicable to clinical practice. Similarly, an even more meticulously standardized analysis protocol could be devised to decrease the variation in ROI selection between readers that seems likely to account for the majority of the variation we saw. Such a protocol could be used to demonstrate a statistically significant benefit to ADC normalization that we did not detect. This may explain the discordance between our findings and other recent reports. Nevertheless, achieving such high reproducibility in clinical practice is notoriously difficult. As such, we believe that in clinical practice and clinical research, normalization is not necessary for valid use of ADC as marker of highly cellular tumor and is not likely to improve correlation with survival.

## Conclusion

Normalization of ADC does not significantly improve correlation with OS in patients with HGG when compared to absolute ADC. This finding suggests that normalization is not necessary for clinical or research ADC analysis in HGG patients.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this retrospective study consent is not required.

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